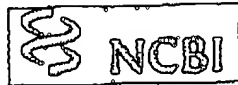


Exhibit D



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1: Hepatology 1998 Oct;28(4):1117-20

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High titers of antibodies inhibiting the binding of envelope to human cells correlate with natural resolution of chronic hepatitis C.

Ishii K, Rosa D, Watanabe Y, Katayama T, Harada H, Wyatt C, Kiyosawa K, Aizaki H, Matsuura Y, Houghton M, Abrignani S, Miyamura T.

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Most cases of hepatitis C virus (HCV) infection result in chronic disease; however, a very small fraction of patients naturally clear the virus and resolve chronic hepatitis. In an attempt to correlate immune response with chronic disease resolution, we compared the antibody response in patients with different outcomes of the infection. Antibody responses to HCV structural proteins were assessed in 34 patients originally diagnosed with acute hepatitis. Five cases resolved acute infection, 22 developed chronic hepatitis, and 7 naturally resolved chronic hepatitis C. To estimate HCV-neutralizing antibodies we used the neutralization of binding (NOB) assay, which evaluates inhibition of the envelope-2 protein-binding to human cells. Enzyme-linked immunosorbent assay was used for the quantitative assessment of serum antibodies. The presence of HCV RNA was ascertained by reverse transcription-polymerase chain reaction. In 6 of 7 patients naturally recovered from chronic hepatitis C, the emergence and the persistence (for more than 3 months) of high serum titers ($>1/600$) of NOB antibodies coincided with virus clearance and clinical resolution of hepatitis. NOB antibody activity was observed in only 2 of 5 patients recovered from acute hepatitis C. Chronic patients who did not show any resolution during the course of the study developed low or no NOB antibodies. Because of the correlation between prolonged high NOB titers and natural resolution of chronic hepatitis C, vaccination or passive immunization aimed at high titers of NOB antibodies may be valuable new therapeutic approaches for chronic hepatitis C.

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